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EDITORIAL COMMENT

Walking With Sir William

Reflections on Collateral Steal, Recruitment, and Ischemic Protection*

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In 1619, Sir William Harvey (1) was the first to contemplate, then demonstrate, the existence of pathways permitting blood to circulate from artery to vein and back again through postulated connections too small to be seen. Of course, these pathways were later proven to be the capillaries and microcirculations which, we now know, form collateral connections in the heart under the right conditions (2–4). This and similar direct observations by Harvey and other Renaissance physicians established the concepts of the circulation of blood and stunned the proponents of Galenic physiology. According to Galen, the overriding forces for bodily function were the liver (responsible for the generation of blood and nutritional growth), the heart (for energy and vital force), and the brain (for sensation and reason) (1). Galenic theory stated that the active phase of cardiac motion was diastole and that the heart did not circulate blood but rather blood movement occurred by an intrinsic pulsatile force residing in the arteries themselves.

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Galenic postulates, often in opposition to direct observations, did not satisfy the Aristotelian mind of Dr. Harvey, who in his description of the function of the heart, "De Motu Cordis," not only pointed out the flaws of Galenic physiology but also convincingly demonstrated with calculations of the blood volume that more blood circulates than exists in a person's entire body and must therefore move in a circuit. Observing the effects of venous filling in the human forearm was a unique physical demonstration of blood flow through arteries and back to the heart from the veins. Walking with his mentors in the courtyards of Padua, Sir William could only dream about future revelations such as those of Werner et al. (5) and Zimarino et al. (6) on coronary collateral function in this issue of the *Journal*.

DETERMINANTS OF CORONARY STEAL

There are three critical conditions needed for coronary steal in man as previously postulated by Gould et al. (7), Schaper et al. (8), and Becker (9), namely, that: 1) the epicardial donor artery resistance is high (with low post-stenotic pressure proximal to the collateral origin during hyperemia; 2) the collateral pathway resistance is not negligible; and 3) the microvasculature distal to the total occlusion is maximally dilated with exhaustion of vasodilatory reserve, thus producing a shift of flow away from the collateral bed with the potential for inducible ischemia.

Using direct measurements of pressure and flow across chronic total occlusions in the catheterization lab, Werner et al. (5) provide direct validation of the three hypothesized interacting factors required to produce steal in the human collateral circulation. In 56 patients, Werner et al. (5) positioned pressure and flow sensor wires across both the occluded artery and a partially occluded contralateral donor artery. This sophisticated and detailed protocol can be admired as much for the difficulty in execution as for the scientific product. Pressure and flow in the collateral and donor regions were measured at base and during hyperemia induced by intravenous adenosine. The collateral coronary vasodilatory reserve decreased (<0.85, "steal group") in 26 patients, remained unchanged in 11 patients, and increased in 19 patients (collateral "recruitment" group). To validate the postulates of coronary steal, the resistance indices of the donor segment as well as the collateral and donor microvascular beds were calculated (Fig. 1). One important new observation was that the lower the fractional flow reserve of the donor artery (i.e., the lower the post-stenotic pressure), the higher the donor artery resistance and the higher the association with steal. Donor and collateral resistances were significantly increased in the steal group compared with unchanged or decreased donor resistance with reduced collateral resistance in the collateral recruitment group (Fig. 2). These data were consistent with previous studies (10–13) and extended the findings by measuring both donor and collateral bed physiology nearly simultaneously.

Study limitations. The limitations of the study by Werner et al. (5) are few. In terms of the elegant design and execution, data acquisition may be difficult, involving careful sensor wire placement and manipulation. Reproducibility of flow and pressure measurements obtained serially in time may be questioned, but given the prior studies and careful positioning, this fault is likely minor. Measurement of collateral flow beyond an occlusion should not be contaminated by antegrade flow, which may occur after wire passage in some patients. The contamination of occlusive flow by antegrade flow may lead to a data error but special care was taken to exclude these patients when angiography indicated that antegrade coronary contrast opacification was present. Collateral volumetric flow was approximated based on flow velocity measurements, relying on fixed recording positions. Alterations of volume flow might occur to some degree owing to heart motion, breathing, and movement artifacts (12). The authors also note that nitroglycerin (NTG), frequently used in other studies to paralyze vasomotion and eliminate the influence of minor diameter

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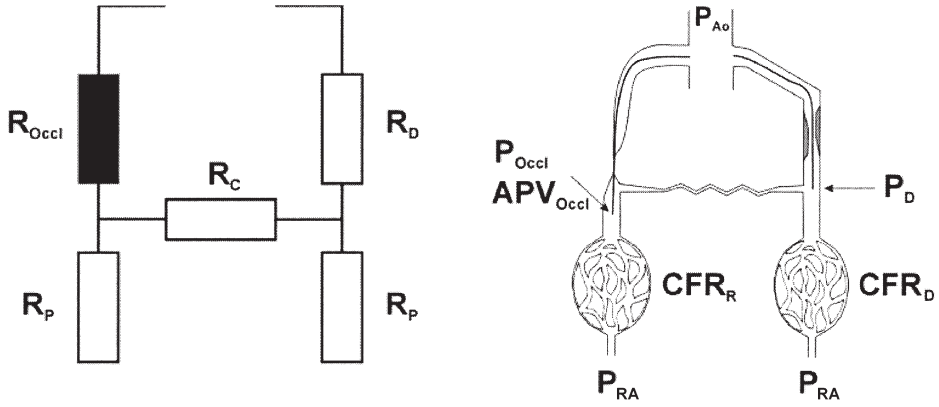

Figure 1. Schematic model of coronary and collateral circulation **(left)** and experimental measurements **(right)**. Aortic pressure (P_{Ao}) is recorded via the guiding catheter. Pressure at the take-off of the collateral in the donor artery (P_D) is recorded before recanalization, as well as the coronary flow reserve in the donor artery (CFR_D). Collateral blood flow velocity (APV_{Occl}) and pressure (P_{Occl}) are recorded distal to the occlusion before balloon dilatation, and CFR_R is recorded in the recanalized artery at the end of the procedure. The resistance of the occlusion (R_{Occl}) is infinitesimal, and resistance indexes are calculated to describe the donor resistance (R_D), collateral resistance (R_C), and microvascular resistance distal to the occlusion (R_P). Reproduced from Werner et al. (5).

changes, was avoided because the NTG-induced hemodynamic changes would adversely affect this particular protocol.

Clinical implications. The study by Werner et al. (5) extends our current understanding of the coronary collateral circulation and as such completes postulated physiology with Aristotelian "hard" data. This study, as well as others (10–14), emphasizes the dynamic nature of the collateral circulation and that the large variability of responses is due, in part, to the interplay of resistances and pressure beyond that of the occluded bed alone. Moreover, this study also points out the potential influence of the donor artery as a target for therapeutic manipulation, with recanalization improving the collateral flow through restoration of donor artery pressure, therefore reducing the potential for coronary steal and myocardial ischemia.

COLLATERAL RECRUITMENT AND DERECRUITMENT

Does the ischemic protective effect of collaterals disappear after recanalization of a chronic total occlusion? Zimarino et al. (6), using pressure sensor guide wires, demonstrated that a rapid decline in the collateral coronary reserve (derecruitment) occurs after recanalization, producing increased susceptibility to myocardial ischemia and an enhanced potential of future ischemic events. The study was performed in 42 patients with chronic total occlusions, measuring the fractional flow reserve (FFR) after a series of consecutive balloon inflations and drug-eluting stent deployments. After each new coronary lumen enlargement, angiographic collateral flow and the sum of ST-segment elevation were correlated with the collateral physiology; measuring both $FFR_{myocardial}$ and $FFR_{collateral}$, percutaneous coronary inter-

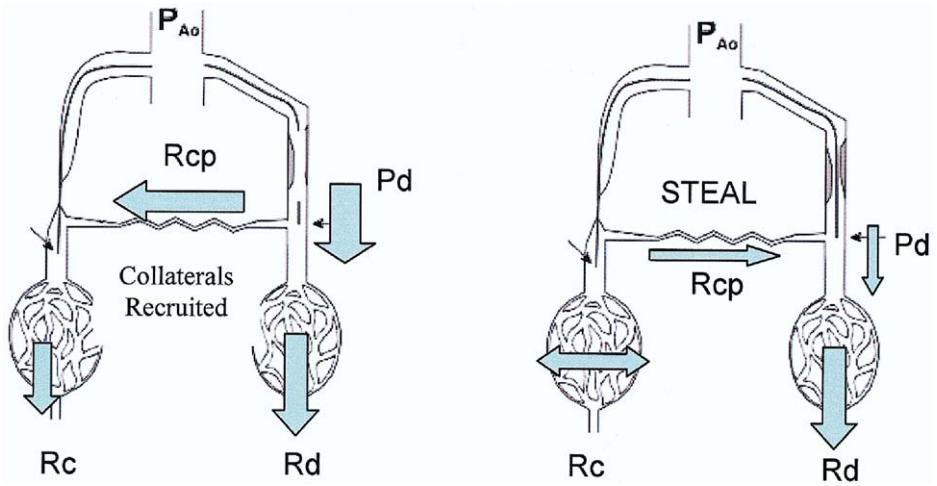

Figure 2. Schematic diagrams of conditions that produce recruitable collateral flow **(left)** and coronary steal **(right)**. Recruitable collateral flow has large donor artery perfusion pressure (Pd) (size of arrow reflects amount of pressure), lower collateral pathway resistance (Rcp), and low collateral bed resistance (Rc). In contrast, collateral steal conditions are associated with a low distal perfusion pressure (Pd or low fractional flow reserve), a higher collateral pathway resistance, and impaired collateral microcirculatory reserve (Rc) (size of arrow reflects amount of coronary reserve); a horizontal arrow means minimal coronary reserve. However, steal can also occur without a donor artery lesion in the presence of an impaired vasodilatory reserve of the microvasculature (14).

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vention improved both angiographic obstruction to flow and antegrade physiologic indices. The rapid restoration of antegrade flow (i.e., normalization of $FFR_{myocardial}$) was associated with derecruitment of the collateral protection as evidenced by increasing ST-segment changes during each repeated coronary flow interruption with balloon occlusion. The authors postulated that rapid collateral derecruitment increases the potential for future ischemic events in susceptible individuals; a conjecture supported by much larger earlier studies of Pijls et al. (15) and Billinger et al. (16). These data emphasize that the collateral bed is not merely a series of passive microconduits but rather a truly dynamic circulation, subject to favorable and unfavorable physiologic stimuli (14).

In addition, Zimarino et al. (6) clarify an important concept when applying the calculations used to identify the functional significance of collateral flow. The two pressure-derived parameters, $FFR_{collateral}$ and the collateral pressure index (CPI = Pw − Pd, where Pw is coronary occlusion pressure, which is measured only during angioplasty balloon inflation, and Pd is donor artery perfusion pressure), describe different features of the collateral circulation. The $FFR_{collateral}$ expresses the collateral contribution to myocardial perfusion, and the CPI evaluates the recruitability of the collateral circulation. Values of $FFR_{collateral}$ <0.25 and CPI <0.30 are associated with provocable ischemia as evidenced by electrocardiogram (ECG) changes during coronary occlusion (15,17–20). Zimarino et al. (6) note that ECG ischemic changes were seen with values of $FFR_{collateral}$ 0.18 and CPI 0.38. Both indices vary inversely with inducible ischemia during balloon inflation, with $FFR_{collateral}$ showing a stronger relationship to summed ST-segment elevation and angina than CPI.

Study limitations. The limitations of the study by Zimarino et al. (6) are notable in that the number of patients is small relative to similar studies (15,16) and the follow-up is not specifically linked to the degree of collateral response. The use of different types of drug-eluting stents adds complexity without important new physiologic findings. The derecruitment of collaterals, although troublesome, was not associated with physiologic responses to predict the individuals at future risk, some of which may or may not be related to the type of stents implanted. Clearly, use of drug-eluting stents for chronically total occlusions will continue and perhaps reduce some of the adverse event rates, independent of the response of the collateral circulation.

CLINICAL IMPLICATIONS

Both Werner et al. (5) and Zimarino et al. (6) remind us that collateral activation is stimulated by myocardial ischemia and its physiologic corollary of low myocardial perfusion pressure (i.e., a high trans-stenotic pressure gradient or low donor FFR) initiating neurohumoral signaling, including angiogenic growth factor release, promoting recruitment and the development of new collaterals (21). It is also noteworthy that the collateral protection appears more developed in patients with preserved regional myocardial function, likely owing to less fibrosis or myocardial scarring due to chronic ischemia or infarction (21).

For the clinician, these two papers shed more light on the protective and provocative role of the collateral microcirculation. The investigations into the coronary circulation with sensor guide wires advance our understanding and may lead to a new paradigm in the treatment of patients with totally occluded vessels and an active collateral circulation. The authors of both studies are to be congratulated for walking with Sir William and keeping us on the path through direct observations, supporting theories that often lead to therapeutic advances for our patients.

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